RESEARCH NOTE

Thirty-day mortality of nosocomial systemic bacterial infections according to antibiotic susceptibility in an 800-bed teaching hospital in France

D. Guillemot[1], I. Gasquet[2], O. Vallet[2], M.-F. David[2], C. Laurent[1] and D. Mathieu[2]

[1]Centre de Ressource en Biostatistiques, Epidémiologie et Pharmacoépidémiologie (CeRBEP) appliquées aux Maladies Infectieuses, Institut Pasteur, Paris and [2]Hôpital Paul-Brousse, Faculté de Médecine Paris-Sud, Villejuif, France

ABSTRACT

Overall 30-day mortality among patients with nosocomial bacterial infections was analysed according to antibiotic susceptibility in an 800-bed hospital. Survival analysis identified three factors associated with an increased mortality rate: (1) a longer interval between admission and onset of infection; (2) bacterial resistance; and (3) the severity of the initial illness in the intensive care unit. The increased mortality rate associated with antibiotic resistance was observed for all bacterial species with the exception of Gram-positive cocci, and remained significant or near-significant regardless of the hospital ward.

Keywords Bacterial resistance, epidemiology, mortality, nosocomial infection, resistance

Original Submission: 27 April 2004; **Revised Submission:** 27 December 2004; **Accepted:** 30 December 2004

Clin Microbiol Infect 2005; 11: 502–504
10.1111/j.1469-0691.2005.01107.x

Few studies of the consequences of nosocomial infections (NIs) caused by antibiotic-resistant bacteria have estimated the resulting excess mortality. This lack of information may undermine the efforts of hospital administrators to target antibiotic resistance. The present study used routine microbiological and administrative databases to analyse the overall mortality rate associated with NIs caused by antibiotic-resistant bacteria in an 800-bed hospital in France.

The microbiology department database was used to identify all bacterial infections documented in hospitalised patients during 1998. Systemic NIs were defined as the first systemic infection in a patient after hospital admission, with an interval between admission and the date of the first positive culture of at least 3 days. Septicaemia was defined on the basis of at least one positive blood culture, except coagulase-negative staphylococci, for which two positive blood cultures were required. Other infections were defined, independently of blood culture, as follows: acute pneumonia on the basis of a positive protected brush sample or bronchoalveolar lavage yielding $>10^4$ CFU/mL; pleural infection on the basis of a positive pleural effusion puncture; and abdominal sepsis on the basis of a positive peritoneal puncture. Lower urinary tract infections without bacteraemia were excluded. The microbiology database was then linked with the hospital's administrative database (patient age and sex, date of admission, vital status at 30 days after the onset of infection). No information was available regarding any antibiotic treatment received by the patient before or after the infectious episode, or on non-vital outcome. Information needed to calculate the mortality-predicting score at admission ($MPM_{(cpr)}$) [1] was recorded for patients hospitalised in the intensive care unit (ICU).

Bacteria were categorised as resistant, intermediately resistant or susceptible to antibiotics, as recommended by the Antibiotic Susceptibility Committee of the French Society of Microbiology [2] and reported routinely to the responsible clinician. Bacteria were grouped as: (1) Gram-positive cocci; (2) *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp. and *Serratia* spp.; and (3) other Gram-negative bacilli. Infections caused by other bacteria were excluded. Methicillin-resistant staphylococci, penicillin G-resistant streptococci, ampicillin-resistant enterococci (no vancomycin-resistant isolates were obtained), cefotaxime-resistant Enterobacteriaceae, *Pseudomonas* spp. resistant to ceftazidime or imipenem (all isolates resistant to fluoroquinolone were also resistant to

Corresponding author and reprint requests: D. Guillemot, Institut Pasteur, 25–28 rue du Dr Roux, 75724 Paris Cedex 15, France
E-mail: guillemo@pasteur.fr

these drugs) and *Acinetobacter* spp. resistant to imipenem were classified as resistant.

Cases involving antibiotic-resistant bacteria were compared to those involving intermediately resistant or susceptible isolates. Univariate analysis was first used to identify predictors of 30-day mortality, using Pearson's Chi-square or Fisher's exact test for categorical variables, as appropriate, and Student's *t*-test or the Mann–Whitney *U*-test for continuous variables. Continuous variables were then dichotomised around the median for univariate analysis of the survival probability in the Kaplan–Meier method with the log-rank test. The multivariate Cox proportional-hazards model of survival was initially constructed with variables with a univariate log-rank p value of < 0.1, followed by backward stepwise regression and the maximum-likelihood method. A subgroup analysis of patients hospitalised in the ICU took into account the $MPM_{(cpr)}$ score [1].

In total, 115 patients were included, of whom 13 were lost to follow-up. Thus, 102 NIs were analysed, comprising bacteraemia (86%), peritonitis (7%), pneumonia (5.5%) and pleuritis (1.5%). Age, sex, hospital ward, and the interval between admission and the onset of infection were not associated with antibiotic resistance. The overall 30-day mortality rate was 18.6%, and was not influenced by age (mean ± SD = 54.6 ± 16.8), sex (66.7% males), the type of infection, the bacterial species or the hospital ward. The mortality rate was 34.2% for NIs caused by antibiotic-resistant bacteria, compared with 9.4% for NIs caused by susceptible isolates (p 0.002). Two factors were associated independently with mortality, namely the interval between admission and infection onset (median 19 days), and infection by antibiotic-resistant bacteria (Table 1). The association between the mortality rate and antibiotic-resistant bacteria was independent of the hospital ward (except in the case of Gram-positive cocci) (Fig. 1).

The 29 NIs identified in ICU patients did not differ from those in non-ICU patients in terms of age, sex, the bacterial species or antibiotic resistance status. The strength of the association in this subgroup between 30-day mortality and antibiotic-resistant bacteria persisted (hazards ratio = 3.7; 95% CI, 0.7–18.9), with a hazard ratio of 4.8 (95% CI, 0.7–18.9) observed with the $MPM_{(cpr)}$ score dichotomised according to the median, despite the lack of statistical significance.

Overall, these results indicated a significant association between antibiotic-resistant bacteria and the 30-day mortality rate in patients with systemic nosocomial infections. This association was observed regardless of the bacterial species involved (except in the case of Gram-positive cocci), and remained significant or near-significant regardless of the ward specialty. Only four methicillin-resistant *Staphylococcus aureus* strains were isolated, which may explain the lack of any apparent association between mortality and antibiotic resistance among Gram-positive cocci. As found in other studies [3,4], the length of hospital stay before NI onset was predictive of antibiotic resistance and mortality. Age was not a risk factor for mortality, possibly because of the limited age range of the patients.

Among ICU patients, the more severe initial illness did not modify the strength of the relationship between antibiotic-resistant bacteria and mortality. Rather than the acute physiology and chronic health evaluation (APACHE) score or the simplified acute physiology (SAP) score, the

Table 1. Univariate and multivariate analyses (Cox model) of factors associated with mortality at 30 days in patients with nosocomial infections (n = 102)

Factor	Unadjusted hazards ratio (95% CI)	p value	Adjusted hazards ratio[a] (95% CI)	p value
Male sex of patient	2.0 (0.7–6.1)	0.2	–	–
Median age of patients	1.2 (0.5–3.0)	0.7	–	–
Antibiotic-resistant bacteria	4.2 (1.6–11.1)	0.004	3.4 (1.3–8.9)	0.02
Median interval between admission and infection onset	3.4 (1.2–9.4)	0.02	2.8 (1.0–7.8)	0.05
Bacterial species				
Gram-positive cocci	1	–	–	–
Escherichia coli, *Klebsiella* spp., *Enterobacter* spp., *Serratia* spp.	0.9 (0.3–2.7)	0.7	–	–
Other Gram-negative bacilli	1.4 (0.4–4.5)	0.6	–	–
Department specialty				
Medicine	1	–	–	–
Surgery	1.0 (0.3–3.3)	0.9	–	–
Intensive care unit	1.8 (0.6–5.4)	0.3	–	–

[a]The terms of interaction were not statistically significant (p > 0.1) and did not contribute significantly to improving the likelihood of the model.

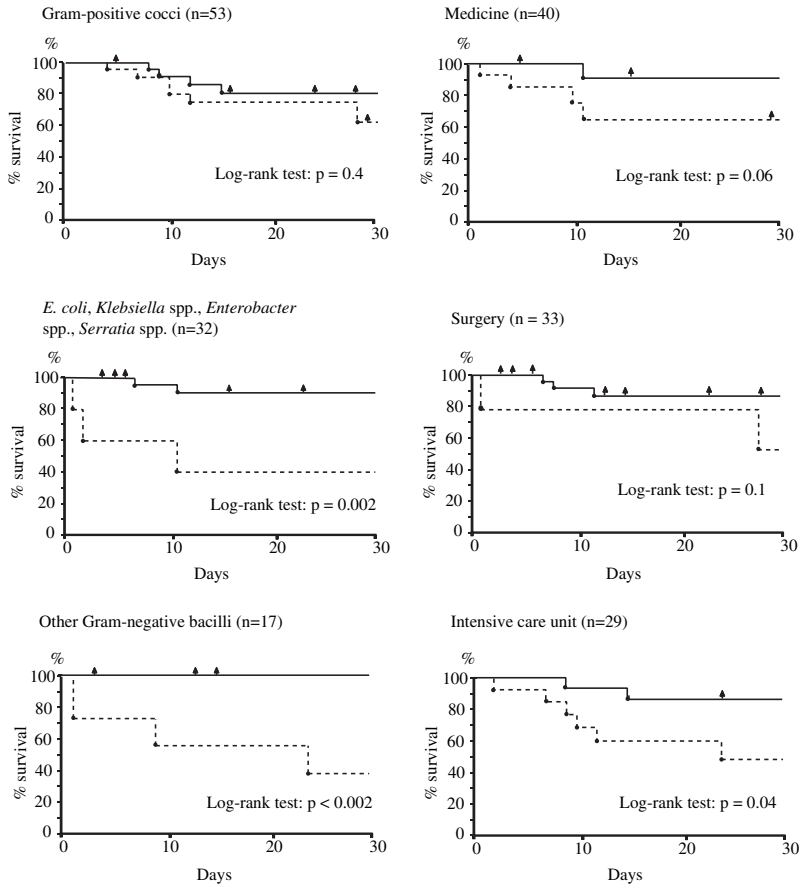

Fig. 1. Survival curves shown as a function of the type of bacterium (left) or the ward specialty (right) for patients with nosocomial infections caused by antibiotic-susceptible (solid line) and antibiotic-resistant (dashed line) bacteria. Circles, time of death; arrows, final time at which patient information was available.

present study used the $MPM_{(cpr)}$ score because of the ease of recording reliable information in a retrospective cohort design, the strong validation of this score's ability to predict death among ICU patients [1], and validation of the score's ability to predict death among ICU patients in the hospital (data not shown).

However, this study has several potential limitations. First, automated databases were used, thereby hindering access to information on disease severity, co-morbidity and/or underlying diseases, and making it impossible to calculate severity scores for patients who were not hospitalised in the ICU. Furthermore, no attempt was made to review the patients' charts in order to determine whether death was directly caused by the infection. Second, it was not possible to analyse the reasons for the observed difference in the mortality rate according to antibiotic susceptibility. Nevertheless, this data-linkage approach could rapidly provide hospital decision-makers with pertinent information on the clinical consequences of nosocomial infections caused by antibiotic-resistant bacteria.

ACKNOWLEDGEMENTS

The authors are grateful to C. Jasmin, C. Minozzi, J. J. Monsuez and F. Saliba for their collaboration. This study was presented in part at the 10th European Congress of Clinical Microbiology and Infectious Diseases, Stockholm, 2000, and at the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, 2000.

REFERENCES

1. Teres D, Lemeshow S, Avrunin JS, Pastides H. Validation of the mortality prediction model for ICU patients. *Crit Care Med* 1987; **15**: 208–213.
2. Antibiotic Susceptibility Committee of the French Society of Microbiology. *Break point for antibiotic susceptibility*. Paris: French Society of Microbiology, 2000.
3. Gleason TG, Crabtree TD, Pelletier SJ *et al*. Prediction of poorer prognosis by infection with antibiotic-resistant gram-positive cocci than by infection with antibiotic-sensitive strains. *Arch Surg* 1999; **134**: 1033–1040.
4. Vanhems P, Lepape A, Savey A, Jambou P, Fabry J. Nosocomial pulmonary infection by antimicrobial-resistant bacteria of patients hospitalized in intensive care units: risk factors and survival. *J Hosp Infect* 2000; **45**: 98–106.